SECTION III
OCCUPATIONAL ASTHMA AND RHINITIS

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INTRODUCTION AND DEFINITION

Asthma is a common disease which affects 8 to 10 million people in the United States. It is high on the list of diseases requiring medical and hospital care and causes considerable loss of work and incapacity. The prevalence of allergic rhinitis is almost certainly higher and results in distress, discomfort, and work inefficiency. The proportion of this large population whose disease is due to occupational exposure is not known with certainty; indeed, accurate prevalences are difficult to determine. Crude overall estimates have varied considerably from 2% of all cases of asthma (20) to 15% of all male cases of asthma in Japan (23). Whichever of these figures is used to assess its impact in the United States, there is no doubt that occupational asthma causes a significant social hardship and a large economic loss.

Occupational asthma and rhinitis are different from the other forms of the disease only in that they are provoked by agents present in the workplace. Precise definitions of the diseases, however, have proven to be difficult. There have been a number of attempts by learned groups to define asthma in strictly objective terms; none have been entirely successful. Particularly difficult has been the differentiation of chronic bronchitis from asthma and the determination of the degree of airways obstruction and the degree of reversibility that must be present in order to make the diagnosis. A joint committee of the American Thoracic Society and the American College of Chest Physicians has provided a clinical definition (1):

> Asthma: A disease characterized by an increased responsiveness of the airways to various stimulae and manifested by slowing of forced expiration which changes in severity either spontaneously or with treatment. The term asthma may be modified by words or phrases indicating its etiology, factors provoking attacks, or its duration.

A panel of the Allergy Foundation of America proposed (3):

> Asthma is defined as recurrent episodes of wheezing or dyspnea characterized by a significant increase in resistance to airflow. Spontaneously or following treatment, periods of complete or almost complete freedom of symptoms occur accompanied by a substantial decrease in resistance to airflow. A person shall be said to have asthma when the following criteria are met: (1) recurrent episodes of wheezing or dyspnea, (2) objective evidence by pulmonary function test of significantly increased resistance to airflow during episodes and of improvement when the patient is symptom free, either spontaneously or as a result of optimum treatment. Several measures of airflow are acceptable: forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), peak flow or maximum mid-expiratory flow. The following standard is tentatively adopted: the measure of flow should be less than 50% of predicted normal during a symptomatic episode whereas it should improve to more than 80% of predicted normal when the patient is symptom free.

The second definition attempts to define a degree of airways obstruction and reversibility. However, the figures quoted are arbitrary and may be considered by some to be unduly stringent, thus excluding some individuals from the diagnosis who genuinely have the disease. In addition, the definition begs the question of what is predicted normal, implying that normal is one figure whereas, in fact, it is a range usually accepted to include 95% of the population. Thus assuming that an individual, before developing asthma, was in the upper 5% of the population with respect to predicted values, he would require

an appreciable decrease in function before his flow rates decreased to less than 50% of the mean predicted normal value. To both these definitions should be added an exclusion—that the symptoms and signs are not due to cardiovascular disease. This is appropriate as paroxysmal nocturnal dyspnea due to left ventricular failure or intermittent small pulmonary emboli may provoke changes very similar to those of asthma.

Occupational rhinitis is easier to define than is occupational asthma. It can be said to be the episodic work-related occurrence of sneezing, nasal discharge, and nasal obstruction. Occupational rhinitis may co-exist with occupational asthma.

LIST OF CAUSATIVE AGENTS

The list of known agents associated with the development of occupational asthma and rhinitis continues to expand and any current list will, of necessity, be incomplete. It is recognized that an individual with an atopic background may become sensitized to virtually any natural product of appropriate antigenicity and particle size. With respect to synthetic agents, atopy is probably of less importance although bronchial hyperactivity in atopics probably makes them more susceptible to agents causing occupational asthma, regardless of mechanism. As new chemical processes are introduced, the list of agents capable of causing occupational asthma becomes longer. Causative agents of natural origin are found in organic dusts. These are inevitably less well characterized than those synthetic chemicals which cause problems. Because of this, the two are considered separately in the following list:

List of Causative Agents

Natural Products

1. Vegetable gums
2. Flax seed
3. Castor bean
4. Soybean
5. Natural glues
6. Animal danders and other animal antigens
7. Coffee bean
8. Insect debris
9. Detergent enzymes
10. Grain dusts and grain products
11. Orris root
12. Flour
13. Papain
14. Mushroom dust and moldy compost
15. Wood dusts
16. Natural resins
17. Animal fat, oil, and products
18. Fish meal and emulsions
19. Tobacco dust
20. Pancreatic extracts

Synthetic Products

Inorganic

1. Platinum, complex salts
2. Nickel salts
3. Chromium salts
4. Sodium and potassium persulphates

Organics

1. *Diisocyanates*
   - toluene
   - diphenylmethane
   - hexamethylene
2. *Anhydrides*
   - phthallic anhydride
   - tetrachlorophthallic anhydride
   - trimellitic anhydride
3. *Amines*
   - aminoethyl ethanolamine
   - dimethyl ethanolamine
   - ethylene diamine
   - paraphenylenediamine
   - diethylene triamine
   - diethylene tetramine
4. *Pharmaceuticals*
   - penicillins
   - ampicillin
   - spiramycin
   - phenylglycine acid chloride
   - sulphathiasole
   - bromelin
   - amprolium hydrochloride
   - sulphone chloramides
5. *Miscellaneous*
   - formaldehyde
   - piperazine
   - organophosphorus insecticides
   - pyrolysis products of polyvinyl chloride
   - alkylaryl polyether alcohol
   - tartrazine
   - products of heated adhesives

OCCUPATIONS AND POPULATION AT RISK AND PREVALENCE OF DISEASE

In order to develop occupational asthma and rhinitis, the worker must first become clinically sensitized either by immunologic or nonimmunologic mechanisms. Sensitization is a function of the dose, characteristics of the agent, and the individual's own responsiveness. The dose of the agents required to sensitize is not known, but is almost certainly higher than the dose required to elicit symptoms in the already sensitized individual. The prevalence of the disease observed in any population thus depends on the interaction of these variables together with the population selection phenomena discussed below.

Sensitization to natural products occurs most readily in the atopic segment of the population which is estimated to comprise between 10% and 20% of the total population (45). This proportion of the work population might, therefore, be expected to have a higher risk of becoming sensitive to organic dusts if suitably exposed. There are serious problems in taking such a simplistic approach. Both pre-employment and postemployment selection affects the constitution of the residual worker population in the involved industries. An atopic individual may personally decide, or be advised, that his risks of occupational sensitization are considerable and so might choose not to work in a particular industry. Even in the absence of a specific sensitization the atopic, because of the hyperirritability, of his airways, may leave a dusty or irritating work environment within a short time of starting work. Both these factors tend to reduce the proportion of the high risk atopic segment of the population in some industries. Loss from the work force of these high risk individuals also prevents accurate determination of the true impact of occupational sensitizers and tends to give a falsely low estimate of prevalence. In occupational asthma caused by synthetic products, these factors probably have somewhat less of an impact as both atopic and nonatopic individuals develop asthma and rhinitis. Accurate prevalence data are, however, confounded by loss from the work force of the sensitized individual who will often seek alternate employment after recognizing the occupational nature of his problems. Factors determining whether a sensitized worker will leave a particular industry also vary. These include the degree of incapacity, the personal investment in terms of training and education, and the availability of alternate employment. Thus the work forces studied represent survivor populations, and this results in misleading prevalences.

It is well recognized that environmental allergens—to which we are all exposed—have differing potencies as sensitizing agents. This also applies to occupational agents although because the dose received is much more variable both within an industry and from industry to industry, it is difficult to separate dose effect from sensitization potency of the agent. In addition, changes in work practices and environmental control will influence observed results.

The prevalence of occupational asthma and rhinitis varies markedly from industry to industry. Animal handlers and breeders have an approximately 6% risk of asthma and a 9% chance of rhinitis by becoming sensitized to the animals to which they are exposed (26); printers, a 19% chance of developing asthma when exposed to gum-acacia (19); and up to a 75% sensitization to bacterial proteolytic enzymes was reported prior to environmental control in the enzyme detergent industry (48). In the case of synthetic agents, toluene diisocyanate has produced prevalences ranging from about 5% to 15% (31). When given sufficiently long exposure, the complex salts of platinum result in virtually 100% sensitization (41). These facts already noted, together with a complete lack of prevalence data with respect to the majority of agents, prevents any assessment of the overall prevalence of occupational asthma and rhinitis. The populations at risk are presented on page 464.

EPIDEMIOLOGY

The questions which epidemiologic studies of occupational asthma and rhinitis need to answer are:

1. What are the prevalences of the diseases in different occupations?
2. Is there a relationship between dose received, either cumulative or peak concentration, and the prevalence of sensitized workers?
3. What is the relative risk of sensitization of nonatopic compared with atopic workers? Are there other personal factors

POPULATION AT RISK

Industry or Occupation	*Agent or Agents*	*Number*
printers, paper products manufacture	vegetable gums	6,000
	natural glues	130,000
grain handlers	grain dusts, insect debris	97,000
lumber & woodworking industries	wood dusts	1,646,000
millers	flour, insect and mite debris	16,000
bakers	flour, insect and mite debris	230,000
veterinarians	animal danders	23,000
animal breeders and handlers	animal danders	2,000,000
	animal antigens	
laboratory workers	animal danders	10,000
	animal antigens	
farm workers	animal danders	4,500,000
	vegetable dusts	
	organophosphorus insecticides	
vegetable oil production	flax seed	1,200
	castor bean	
	cotton seed	5,500
detergent industry	proteases	5,700
food additive production	proteolytic enzymes	?
	tartrazine	14,000
coffee processing	green coffee beans	12,900
*beauticians/cosmetologists	orris root	?
	paraphenylene diamine	1,000
	sodium and potassium persulfate	13,500
**hospital workers	formaldehyde	275,000
	pharmaceuticals	
	penicillin	3,500
	ampicillin	1,300
	sulphatriazole	1,000
†pharmaceutical workers	penicillin	6,000
	ampicillin	2,000
	spiramycin	?
	phenylglycine acid chloride	?
	sulphathiazole	1,000
	bromelin	?
	amprolium hydrochloride	?
	sulphone chloramides	?
	piperazine	700
solderers, electrical and electronic industry metal fabrication	colophony resin	—
	amino ethyl ethanolamine	1,500
	alkyl aryl polyether alcohol	2,000

POPULATION AT RISK (Continued)

Industry or Occupation	*Agent or Agents*	*Number*
††leatherworkers	formalin	11,000
	chromium compounds	2,000
platinum refiners	complex salts of platinum	300
metal platers	salts of nickel	10,000
	salts of chrome	1,400
fur dyers	paraphenylene diamine	4,000
paint sprayers	dimethyl ethanolamine	3,700
	diisocyanates	10,000
plastics industry	diphenyl methane diisocyanate	1,000
primary manufacture and use:	hexamethylene diisocyanate	500
mainly epoxy resins and polyurethane	phthallic anhydride	4,000
	tetrachloro phthallic anhydride	20
	diethylene triamine	5,000
	diethylene tetramine	100
	piperazine	500
rubber industry	ethylene diamine	5,000
	diisocyanates	2,000
foundry industry	diphenylmethane diisocyanate	1,200
insulation workers	diisocyanates	3,000

*There are 280,000 beauticians in the United States; most are not associated with exposure to listed agents.
**There are approximately 2.5 million hospital workers in the United States.
†There are 112,000 pharmaceutical workers in the United States.
††There are approximately 20,000 workers in the leather processing industry.

which relate to the risk of becoming sensitized?

4. What is the long-term prognosis of sensitized workers who cease exposure?

Though there is a large literature relating to occupational asthma and rhinitis, this consists largely of case reports and detailed investigations of the involved mechanisms. Essentially, the four questions posed above remain unanswered.

Prevalence data are difficult to obtain and require large, complex, and expensive surveys. Prevalences have been reported from some industries, but invariably there are serious problems in interpretation. A major problem is that the populations studied are survivors of the effects of the work environment, sensitized individuals having already left the industry before the study commences. In a follow-up study of a TDI-exposed population, Wegman et al. found that only 45% of their original study group was still employed (47). Of those who left, 80% did so voluntarily; how many for reasons of sensitization is not known. The extent of this attrition of worker populations can thus be large and effectively prevent realistic estimates of sensitization rates.

Prevalence data are often generated by questionnaire studies. While these can provide estimates of the impact of the working environment on the respiratory tract, they do not provide reliable information concerning the prevalence of asthma. The main reason is that questions relating to dyspnea, chest tightness, cough, and wheezing do not differentiate asthma from chronic obstructive pulmonary disease. A study of 300 grain elevator workers provided prevalences of 76% cough, 49% chest tightness, 42% wheezing, and 45% dyspnea (15). This clearly shows that grain dust frequently causes respiratory problems but does not indicate the proportion of the symptomatology due to grain dust related asthma.

There is general agreement that reversible airways obstruction is the prime characteristic of asthma. Pulmonary function surveys of worker groups have been conducted; however, almost invariably, measurements were made at only one time. An index, such as the ratio of the FEV_1 to FVC, will provide evidence of airways obstruction but without any information concerning reversibility. There is thus no way to differentiate the nonreversible airways obstruction of chronic obstructive pulmonary disease from asthma if workers are only studied once. Pre- and post-shift measurements are essential. A comparison of two studies of meat wrappers' asthma due to the pyrolysis products of PVC will serve to illustrate the problem of relating questionnaire data to objective airways changes. Using questionnaire data, Andrasch et al. reported a prevalence of 69% of respiratory symptoms in 96 exposed workers (4). They proved that heated PVC could cause decrements in flow rates in small number of workers by bronchial provocation testing. It is, however, not possible to extrapolate this observation and to account for all or most of the respiratory symptoms in the overall worker group by assuming that they likewise developed airways obstruction on the job. This is shown by a study of a different group of 30 meat wrappers by Krumpe et al. (24). In addition to questionnaire data, they carried out detailed pulmonary function testing after a two-day vacation and again after working one shift or working for the whole week. By questionnaire, 23% of the wrappers reported work-related asthmatic symptoms; however, significant changes in parameters of airflow were not found following exposure on the job in any worker. Both these studies lack measurements of exposure to fumes. Peters et al. reported decrements in flow rates over a shift in workers exposed to TDI (38). They found a mean fall in FEV_1 for the whole group of 0.19 liters. This illustrates two problems: first, the reporting of group mean changes does not provide evidence of the prevalence of asthma, nor, second, how much of a decrement over a shift is needed to make a diagnosis of occupational asthma. The mean decrement reported is very small and though statistically significant, is of the same order of magnitude as the upper limit of variability of a single spirometric measurement. There is a need to develop some generally agreed upon criterion of function decrement in order to determine the prevalence of asthma in worker populations; statistically significant change does not provide a satisfactory definition.

There is even less good information available to answer the remaining three questions. There is evidence that decreases in environmental concentration of agents results in lower prevalences of sensitization to TDI (40), and that control of environmental *B. subtilis* enzymes in the enzyme detergent industry has reduced sensitization (28)(48). There is, however, no available study of any agent which fully answers the question of the relationship of sensitization rate and exposure.

Most studies of sensitization to naturally occurring agents indicate that the atopic segment of the population is at greater risk of sensitization than the nonatopic. Nonatopics may, however, sometimes develop occupational asthma due to exposure to natural products. With respect to synthetic agents, atopy appears to be a much less significant risk factor. There is need for considerably more research in this area to evaluate the likely impact of pre-employment screening. What little data are available on the long-term effects of occupational asthma after ceasing exposure are considered in the section on prognosis. It will be seen from this short account that information is incomplete on the epidemiology of occupational asthma and rhinitis.

PATHOLOGY

Although the amount of available evidence is scant, occupational asthma is considered to be pathologically identical with asthma in general. The pathology of asthma has been studied from three main sources:

1. Autopsies of individuals dying in status asthmaticus, and occasional autopsies carried out on individuals with active asthma who have suffered a traumatic death. The limited amount of the latter material shows less severe changes than those found in status asthmaticus but confirms the essential findings.
2. Biopsy material taken during acute asthmatic attacks and when in remission. This material is limited for obvious reasons.
3. Studies of sputum samples, particularly by section rather than by smear.

The following account is derived from a composite of these sources. The essential path-

ological change found in asthma is a reduction in the lumen of the bronchial and bronchiolar airways. Partial obstruction of an airway results in a nondestructive "physiologic" emphysema with resulting over-distention of the lung. Complete obstruction produces focal areas of collapse which are commonly found in individuals dying in status asthmaticus. Narrowing of the airways is due to bronchial muscle spasm, to an increase in the thickness of all layers of the airways, and to obstruction of the lumen by plugs of viscid sputum. Histologically there is increased thickness of the bronchial muscular layer which is a useful point in the differentiation of chronic asthma from chronic bronchitis. Bronchial mucous glands are hypertrophied and the mucosa is thickened. The thickening is due to a combination of edema, capillary dilatation, and cellular infiltration in the submucosa. The cellular infiltrate is mixed, and includes eosinophils, plasma cells, and lymphocytes. There is characteristically marked thickening of the basement membrane of the bronchial mucous membrane (16). Immunoglobulins, particularly IgM, and the third component of complement have been demonstrated in this region in some patients (8)(9). In severe asthma and in status asthmaticus there is appreciable shedding of mucosal cells into the lumen of the bronchus. The epithelium may lose virtually all columnar cells and consist only of basal cells. Experimental evidence suggests that in remission, a completely new epithelium may develop from these residual basal cells (49). The lumina of the bronchi contain plugs of sputum. In asthma, this has a characteristic nonhomogeneous appearance on staining and contains mucus, a serous exudate, shed epithelium, and inflammatory cells—particularly eosinophils. The sputum may contain creola bodies (clusters of shed epithelial cells) and Charcot-Layden crystals (elongated hexagonal, bipyramidal crystals derived from eosinophils). Examination of expectorated sputum in the living asthmatic will reveal these components and also may show Curschmann's spirals which are casts of small airways. Although there is a paucity of data on the anatomy of the asthmatic airways between attacks, available evidence indicates there is little residual abnormality in the bronchial mucous membrane at this time.

PATHOGENESIS AND PATHOPHYSIOLOGY

Research in recent years has resulted in a much clearer understanding of the pathogenesis of asthma in general; research into occupational asthma has contributed much to this understanding. The pathogenetic mechanisms of asthma are highly complex and which of the many abnormalities demonstrated is of greatest importance is not known. Further, in many cases of asthma the mechanisms are still unexplained. There are three main mechanisms involved in the generation of asthma.

Irritant Factors

Hyperreactivity of the airways as evidenced by methacholine and histamine provocation challenge testing is characteristic of the asthmatic state. Thus an asthmatic responds to between one hundredth and one thousandth of the dose of these agents which will produce airways narrowing in a normal individual. Though the reactivity is greatest when an individual is suffering recurrent asthma attacks, the hyperreactivity remains between attacks although it may diminish. Atopic individuals who have not suffered from asthma for a long period of time show reactivity midway between normals and active asthmatics. In occupational asthma, this decrease in hyperreactivity has been demonstrated following removal from the agent in question. The reasons for the hyperreactivity of the airways in asthmatics are not known; however, it is generally considered to involve an alteration in the homeostatic mechanisms which control the airways' smooth muscle tone. As a consequence of this hyperreactivity, any irritant agent—such as an organic dust or a chemical which may have little or no effect in healthy people—can precipitate episodes of airways obstruction in workers either with asthma or with a past history of asthma. Such episodes can occur even though the agent is present in very low concentration. A mechanism involving stimulation of irritant cough receptors by inhaled material and mediation by the vagus nerve is prominent among those pathogenetic processes producing airways obstruction in asthmatics. For example, the increase in airways obstruction following inhalation of some irritants can be inhibited in ex-

perimental animals by blockage of the vagus nerve. In man, prior inhalation of atropine followed by the inhalation of the irritant would also abrogate the response (30). Based on anecdotal evidence, it is likely that many agents can induce airways obstruction in asthmatic subjects by means of such irritant receptor stimulation. The same agents may act as both irritants and sensitizing agents under different conditions. For example, the inhalation of large amounts of green coffee bean or grain dust may result in an irritant type of rhinitis and conjunctivitis, possibly with some minor airways obstruction. But repeated inhalation of small amounts of these substances may sensitize (22). In the latter case, re-exposure to minute concentrations incapable of producing an irritant effect, will result in upper and lower airways symptoms in these individuals based on IgE mediated allergic effect. Similarly, high concentrations of toluene diisocyanate will cause mucosal irritation in any worker but a "reactor" will respond to barely detectable levels (7).

Allergic Factors

IgE mediated allergic reactions have been strongly implicated in the pathogenesis of many forms of occupational asthma due to natural inhalants and in some due to synthetic chemicals. Epidemiologic surveys employing skin test reactions and respiratory questionnaires have also indicated a positive association between the atopic predisposition and susceptibility of bronchial constriction in the case of natural inhalants. This association between atopy and sensitization to occupational agents has not been as clearly shown in the case of synthetic chemicals, and many individuals with definite asthmatic responses to simple chemicals give no past history of allergic problems in either themselves or in their families. In IgE mediated asthma, there is generally a latent period of weeks, months, or even years between initial contact with the occupational agent and the development of overt symptoms. Only a small proportion of those individuals exposed (i.e., mainly those with a genetically determined predisposition to produce specific IgE antibodies) will generally develop the disease in the case of naturally occurring occupational sensitizers. Skin prick or intradermal tests with the appropriate natural occupational product or allergen are almost always positive as are passive transfer studies in man or primates. Specific serum IgE antibodies have also been demonstrated by *in vitro* tests employing a number of natural occupational agents such as coffee and castor beans (22). In the case of synthetic sensitizers, skin tests may present a problem in that the agent may be very irritating. In some situations, conjugation of the chemical to a carrier protein (such as human serum albumin) has enabled positive skin tests to be demonstrated in some of these individuals and again specific serum IgE antibodies have been demonstrated. IgE antibodies may be measured by several assays, the most common of which is the radioallergosorbent test (RAST). The presence of circulating IgE antibodies seems to correlate well with the development of immediate or early onset asthma due to natural products but not with the late onset type of asthma. Where demonstrated, as against phthallic anhydride (27), trimellitic anhydride (50), and the complex salts of platinum (13), IgE antibodies directed against synthetic chemicals usually correlate well with the clinical presentation. Tolyl-reactive antibodies have been demonstrated in some reactors to TDI (21), but in many others they are undetectable, suggesting the possibility of two different mechanisms of sensitivity reaction to this agent.

The mechanisms involved in late onset asthma, with a lag period of several hours between exposure and onset of symptoms, are not clearly understood. IgE mediation has been suggested by some researchers in the case of late reactions to pollens (42), but this is by no means certain. It is possible that the use of tests to detect circulating immune complexes and the rheumatoid factor, and studies of antibodies of the homocytotropic short-term sensitizing IgG type (5)(33) may shed some light on the mechanisms involved in this more insidious late onset occupational asthma. This remains conjectural. The same can be said for *in vitro* assays for cell-mediated immunity by testing for lymphocyte transformation and the macrophage migration inhibition factor (MIF) production which also might theoretically be associated with some forms of late onset occupational asthma. In IgE mediated asthma and rhinitis, symptoms result from the classic and well known release of mediators from tissue mast cells and basophils subsequent to IgE and antigen interactions at the cell surfaces (39). These mediators include, among others, the slow reacting substance of anaphylaxis (SRSa, now refer-

red to as leukotrienes) histamine, and the eosinophil chemotactic factor of anaphylaxis (ECFa). These act on secondary target tissue to produce the clinical picture of asthma and rhinitis. They act primarily on vascular endothelium to produce edema, by inducing infiltration of inflammatory cells into the mucous membrane, in addition to directly causing smooth muscle spasm. This type of IgE dependent mediator release is noncytotoxic and essentially represents a form of immunologically induced secretion from mast cells. From a biochemical viewpoint, the studies of mediator release employing human lung tissue agree with those obtained using lung tissues from other species, human peripheral leukocytes, and rat peritoneal mast cells. The union of an antigen with IgE at the cell surface is followed by an intracellular calcium-requiring activation of an esterase followed by autocatalytic feedback activation of a proesterase and an energy requiring step which utilizes glycolysis or oxydative phosphorylation. This is followed by an intracellular step requiring calcium, a step supressed by increased concentrations of cyclic adenosine 3', 5' monophosphate (cyclic AMP), and finally the secretion of mediators. It is thought that IgE receptors act as a concentration mechanism which juxtaposes two molecules of this trace immunoglobulin side by side to permit bridging by the antigen. Such bridging is held to produce a membrane perturbation which initiates the sequence of events.

Pharmacologic and Other Mechanisms

The occupational causation of asthma by some agents has been clearly demonstrated by carefully controlled bronchial provocation tests, yet the pathogenetic mechanisms involved are still unknown. In some of these cases, bronchial hyperreactivity to methacholine has been demonstrated, but this is likely to be a secondary phenomenon rather than the initiating mechanism because a return toward normal occurs following avoidance of the agent (25). With other agents, immunologic hypersensitivity may be involved, but the evidence available is either conflicting or very scanty. For instance, in asthma due to synthetic chemicals, the appropriate reactive group may not be present on the protein-hapten conjugates used for the tests, or the simple chemical may alter host proteins to create neoantigens which induce a subsequent immune response. In the case of some organic dusts, the causative antigen may represent only a minor component rendering both skin and *in vitro* tests relatively insensitive.

To explain the pathogenesis of asthma due to these agents, direct pharmacologic action on the airways and nonimmunologic release of histamine and other spasmogens has been postulated. *In vitro* experiments have shown the direct release of histamine by the complex salts of platinum (34) and by aqueous extracts of western red cedar (18). However, more recent evidence has demonstrated specific IgE sensitivity both by passive transfer in man (37) and by RAST test (13) in the case of the former. Grain dusts have been shown to have the potential to activate the alternate pathway of complement, with the potential for nonimmunologic release of mediators from mast cells by the anaphylotoxins generated by this reaction (32). Toluene diisocyanate has been shown by *in vitro* testing to act as an inhibitor of the stimulation of beta adrenergic receptors (6)(16), thus raising the possibility that it could interfere with autonomic control of airways tone in the direction of favoring bronchoconstriction.

These hypothetical mechanisms raise two major questions. Why does only a proportion of the exposed population respond? Why is there a latent period between first exposure and the development of symptoms? Attempting to answer the first question, it could be suggested that the known hyperirritability and hyperresponsiveness of the airways of an atopic individual would be expected to result in a response to a much smaller release of mediators than would a nonatopic individual. Under these circumstances only the atopic segment of the population should respond in this way. Yet there is no doubt that, though less common, occupational asthma does occur in nonatopic workers. In order to support this hypothesis, some mechanism must be demonstrated which results in the airways of a nonatopic individual becoming more nonspecifically reactive. Or there is a genetically determined factor, not associated with atopy, which determines bronchial hyperreactivity. The second question concerning latent period is difficult to answer. There is an implication of a nonimmunological change in airways, responsiveness between first exposure and first development of symptoms. There is no information to explain how this is brought about. However, possible theoretical mechanisms ex-

ist which may account both for the latent period and for the occurrence of changes in nonspecific reactivity in nonatopic individuals. One author has noted that some individuals with occupational asthma give a history of what sounds like a respiratory virus infection a short time before the onset of work-related symptoms. This information, by its very nature, is nonobjective and could be inaccurate. It has been demonstrated that the airways of the nonatopic become hyperactive in a similar way to the airways of an atopic individual following respiratory infections (17). Thus a change in airways reactivity following an infection could lead to a self-perpetuating asthmatic condition when repeatedly triggered by an industrial agent. This mechanism could account for both the occurrence of asthma in the nonatopic and also for the latent period, the latter being the time between the first exposure to the occupational agent and the first occurrence of an appropriate respiratory infection. Similarly, the airways of an atopic become more sensitive to methacholine following challenge by an allergen to which he is sensitive (12). The airways of an atopic individual may, therefore, vary considerably in their nonspecific responsiveness, depending on the presence or absence of aeroallergens in the nonwork environment. Coincidental exposure to an aeroallergen, which in itself may result in mild or subclinical effects, and an occupational agent could result in an asthmatic attack. The hyperreactive state initiated by the environmental aeroallergen could then be perpetuated by continued industrial exposure even after the aeroallergen was no longer present. Though attractive, there is no evidence to directly support this hypothesis.

CLINICAL DESCRIPTION

Types of Asthmatic Reactions Associated with Inhalation of Occupational Products

Provocation challenge testing with many types of occupational products has resulted in different patterns of airways response. These are immediate responses, occurring within minutes of exposure; nonimmediate, or late responses, which have a latent period of several hours between exposure and first airways changes; biphasic responses which are a combination of both early and late; and at times, sustained or recurrent asthmatic reactions (35). There is no difference in the clinical manifestations of these reactions and those noted after experimental inhalation of natural common aeroallergens such as pollen and mold. The experimental asthmatic reactions are thought by most investigators to serve as the clinical laboratory correlates of the immediate and late asthmatic reactions which are noted in an ordinary clinical setting.

Symptoms, Signs, and Natural History

Symptoms are characterized by dyspnea, wheezing, chest tightness, and cough of an episodic nature. The history, however, provides the most important diagnostic clue, and the aphorism "listen to the patient, he is telling you the diagnosis" truly applies in the context of occupational asthma and rhinitis. Immediate reactions usually occur within 10-20 minutes after exposure and may last for several hours or until leaving work. They are usually not associated with systemic reactions or marked changes in the white blood cell count and are characterized by only moderate or slight eosinophilia. They are reversible by isoproterenol and can be inhibited by prior inhalation of cromolyn sodium but not by inhaled corticosteroids. The occurrence of late reactions, after the worker has returned home, often makes diagnosis and recognition of occupational asthma more difficult. In some late reactions, bronchospasm may be reflected by cough, chest tightness, or dyspnea without significant wheezing—possibly indicating small airways obstruction. In general, late reactions develop slowly and become progressively worse. They may not be clinically obvious except on exertion or until fully developed. They may require a latent period of 4-8 hours before appearing and may last from 24 to 96 hours. These reactions may also be associated with systemic symptoms such as malaise and myalgia. Fever and leukocytosis may be present, especially if a systemic reaction occurs, and there may be marked eosinophilia. Late reactions are, as a rule, poorly and only temporarily reversible by isoproterenol. They are, however, reversible by inhaled or systemic corticosteroids and may be prevented by the prior inhalation of cromolyn sodium. Although the taking of a careful occupational history can often uncover symptoms suggestive of occupational asthma, other diagnostic tests depend on the availability of proper facilities. For example, in the case of bronchial provocation challenge testing, or *in vitro* and related tests, facilities and adequately trained personnel (to perform these procedures) are often lacking in many medical centers.

Appropriate Laboratory Investigations

Pulmonary Function Studies

Demonstration of reversible airflow obstruction is a prerequisite for making the diagnosis. Determination of the forced expiratory volume in 1 second (FEV_1) or other indices of flow rates (such as the forced expiratory flow between 25% and 75% of the forced vital capacity (FEF_{25-75})) are relevant and reproducible tests. The latter determination is more sensitive but has greater variability. Regardless of the test employed, measurements should ideally be made both before and after work exposure. The most frequently employed function tests used to detect an asthmatic response in workers are those that involve demonstration of limitation in maximal expiratory flow rates either by traditional volume/time plots or by maximal expiratory flow/volumes curves, using an electronic spirometer or pneumotachagraph. These tests have also proven useful in field studies. Many centers have included relatively newer methods of detecting airways obstruction (such as closing volume) in their epidemiologic field testing procedures. The additional benefits from these newer tests are not certain. Proper timing in the use of pulmonary function tests may also be crucial in the diagnosis of occupational asthma. Measurement of both pre- and post-shift ventilatory function of the worker usually demonstrates an acute asthmatic effect resulting from exposure under normal job conditions. In interpretating these data, account should be taken of the normal diurnal variation in ventilatory function.

Bronchial Provocation Tests

Two types of bronchial challenge tests are useful in the diagnosis of occupational asthma. These measure either nonspecific bronchial reactivity to methacholine or histamine, or specific reactivity to the agent in question. Demonstration of nonspecific airways hyperirritability tends to confirm that the worker's complaints are real and that he does, indeed, have asthma. Methacholine challenge should be carried out using the protocol developed by the program directors of the Asthma and Allergy Disease Centers (10). Challenge with a specific agent provides a means of proving the occupational nature of the worker's asthma. This is important if a change of job is being considered and can be important for medico-legal reasons. In addition, other less direct approaches such as demonstration of specific IgE mediated skin reactivity or RAST testing are not available with respect to many agents. The object of the challenge is to mimic, under controlled conditions, workplace exposure and to monitor ventilatory function before and for several hours (preferably at least 24) afterwards. Concentrations of the agent should be measured and should not exceed those to which the worker is exposed in the workplace. It is essential to carry out a similar procedure with a control nonirritant, nonsensitizing material in order to evaluate any changes in pulmonary function observed with the test agent. A decrease of 20% in FEV_1 is a commonly used criterion for positive reaction.

Chest Roentgenograms

Chest roentgenograms are not of particular value in the diagnosis of occupational asthma and may only reveal the overinflation often found in asthma. They may, however, be of considerable importance in differentiating late onset asthma from hypersensitivity pneumonitis, which can present a similar clinical picture.

Skin Tests and RAST

In occupational asthma, skin testing can be of considerable diagnostic value where immediate wheal and flare hypersensitivity is involved and sufficiently purified skin test preparations are available. Skin testing can be helpful both in assessing the atopic status of the worker by using common aeroallergens and in attempting to determine the presence of a specific IgE antibody against the appropriate occupational agent. Any natural agent employed for skin testing purposes should be as well characterized and as purified as possible. This presents an enormous problem with some organic dusts because of their complexity. It is sometimes possible to use nonnatural agents in a very pure form as, for instance, ammonium hexachloroplatinate (36); others, such as dimethylethanolamine may produce wheal and flare responses in all individuals tested (46). Conjugation of a reactive chemical to a carrier protein, such as human serum albumin, can usually provide a usable skin test preparation. All skin test antigens should be nonirritant and nontoxic to normal individuals in the concentrations to be employed. They should always be evaluated initially

in very low concentrations, employing the prick assay rather than the intradermal method. While skin testing is more sensitive in demonstrating IgE mediated reactivity than *in vitro* methods such as RAST, the latter does have some advantages. It avoids the potential danger of a serious reaction following skin tests and is useful in individuals on medication which might interfere with skin reactivity or who have skin problems such as dermatographia or eczema which interfere with skin test interpretation.

Treatment and Prognosis

The treatment of occupational asthma does not differ from that of conventional asthma due to environmental pollens and molds. Basically it consists of the avoidance of known causative inhalants and the control of symptoms with conventional bronchodilators (preventives such as cromolyn sodium and corticosteroids if necessary). With proper diagnosis and permanent removal from the offending environment, the prognosis is good. The ultimate form of treatment in occupational asthma is removal of the affected worker from the job environment which, in effect, will usually result in a "cure." Symptoms will usually subside within a few days of ceasing exposure; however, this is not invariably the case. There is a lack of data on follow-up of occupational asthmatics who cease exposure. Collection of such data is fraught with difficulties. Patients are "lost" when they move to change employment, and some refuse to cooperate, particularly if litigation against a previous employer is involved. Some individuals with TDI induced asthma continue to complain of attacks long after leaving the industry. Is this a long-term effect of occupational asthma, or is it asthma of some other causation? Comparison of pre-employment function tests with similar tests carried out in 20 workers, who had ceased exposure to TDI from between 3 and 8 years because of sensitization, was made by Adams (2). Twelve of the 20 had FEV_1 and FVC values unchanged from their pre-employment levels; 6 had decrements up to 10% and 2 had larger decrements. Symptoms of dyspnea on exertion and chest tightness were reported by those with decrements of function. Thirty-eight workers with proven occupational asthma due to western red cedar were studied by Chang-Yeung (11). While the majority became symptom-free, eight continued to suffer recurrent asthma attacks when evaluated after a mean of 1.6 years following cessation of exposure. It is of interest that seven of the eight were nonatopic and all but one gave a biphasic response on challenge at the time of diagnosis as compared with 50% of those who became symptom-free. There is a great need to develop data concerning the fate of occupational asthmatics when they cease exposure.

In cases where workers cannot be totally removed from the environment, a trial of a preventative such as cromolyn sodium or the long-term use of a theophylline preparation or inhaled corticosteroid might theoretically prevent immediate or late bronchial reactions. This form of preventive therapy is obviously no substitute for removal of the worker from the hazardous environment. Even though engineering methods and other dust and vapor suppressant measures are often effective in lowering workplace concentrations of the agent it must be recognized that in a sensitized worker even minute amounts of occupational agents can result in a response.* In this context, occupational standards such as 8-hour time-weighted-averages and ceiling levels have little or no meaning. In some situations temporary protection can be provided by the use of a respirator, however, this should not be considered as a long-term solution. If preventive and therapeutic measures are not effective, a final and agonizing decision often must be made involving the selection of another job for the worker. This often produces adverse domestic, financial, and family problems and provides multiple legal complications.

DIAGNOSTIC CRITERIA

History

The mainstay of diagnosis in occupational asthma remains that of obtaining a careful history and asking the all-important question "What is your occupation?" In view of the wide variety of agents that cause occupational asthma, many such cases will only be diagnosed if the possibility of a cause and effect relationship is first entertained and then sought by careful questioning. Occasionally, nocturnal cough rather than wheezing during the working day may be the presenting symptom. In other cases, symptoms may extend over the weekends and short holidays, effectively disguising the industrial ori-

*In rare cases, a level of exposure may be demonstrated at which flow limitation does not result.

gin of the disease. Education of physicians in the occupational causation of asthma and rhinitis is the key to more frequent recognition of this group of diseases.

Pulmonary Function Tests

Airflow obstruction upon exposure to an offending industrial agent, with reversibility, is a prerequisite for diagnosis. Ideally, such measurement should be made both before and after work exposure. While decrements of function strongly suggest the occupational origin of the asthma, they do not necessarily indicate which agent is responsible. This can be particularly difficult in a complex environment. Additionally, there is no general agreement on what decrement of function over a work shift is necessary to make a diagnosis of occupational asthma.

Bronchial Provocation Testing

Performed under properly controlled conditions, this remains the most certain way of confirming the occupational nature of a workers asthma and of identifying the inhaled agent involved. Such provocation testing can clearly establish a cause and effect relationship but does not provide information with regard to the pathogenetic mechanisms. In performing such challenge testing one should carefully attempt to simulate the subject's work conditions with monitoring of exposure levels.

Skin Tests, RAST, and Precipitating Antibodies

Skin, prick, and intradermal tests are often useful both to assess the atopic status of a worker and to look for the early development of IgE mediated wheal and flare skin reactivity against the appropriate offending agent when an IgE mechanism is involved. Unfortunately, suitable skin test preparations are not available for many agents either because they are too irritant in themselves or too impure. *In vitro* procedures to detect IgE antibodies such as the radio allergosorbent test (RAST), enzyme-linked immunoassay, or polystyrene tube assay are also assuming increased importance in the diagnosis of occupational allergic disease. RAST is less sensitive and, therefore, of somewhat less value when compared to the skin test, but it does afford many advantages, including that of a noninvasive *in vitro* technique. Tests for the presence of IgG precipitating antibodies against organic dusts and related natural products have generally not been useful in the diagnosis of occupational asthma. Precipitins, when present against organic dusts, are generally detected in both symptomatic and nonsymptomatic workers and often do not correlate with the presence of overt disease. They tend to correlate better with the extent of exposure (43).

METHODS OF PREVENTION

Prevention of occupational asthma and rhinitis will be considered under four headings.

1. ***Recognition that a problem exists.*** The list of known agents which can cause occupational asthma and rhinitis is long and is continually growing. It is important that the hazards associated with exposure to these agents are known, both by management and labor, so that appropriate steps may be taken. As it is inevitable that more sensitizers will be recognized in the future, industry must develop rapid and practicable means to detect them. Unfortunately, animal tests are not likely to be of value in this context.
2. ***Prevention of sensitization.*** There are two approaches to the prevention of sensitization, neither of which is entirely satisfactory. The impact of occupational sensitization falls most heavily on the atopic segment of the population. It is possible to conduct pre-employment screening to determine the atopic status of job applicants by family and personal medical history and by carrying out skin tests with a number of common aeroallergens. Such pre-employment screening should result in a much lower prevalence of occupational asthma and rhinitis, particularly following exposure to natural products. It is doubtful if it would have a significant impact on asthma and rhinitis due to synthetic agents. Though not strictly covered by the Equal Employment Opportunity laws, the exclusion of such a large segment of the population from work in certain industries might be considered discriminatory.

   While an atopic individual is likely to become sensitized following continued exposure to even minute amounts of a

natural product, sensitization in nonatopics may be dose-related. In both atopics and nonatopics, sensitization to synthetic agents may also be dose-related. There is a lack of objective studies to support this opinion, mainly because of the great difficulty in conducting such studies. Thus continuous personal exposure monitoring will be needed over a period of a year or more with follow-up of ideally 100% of the workers. Such a study is difficult to achieve. Changes in the prevalence of reported sensitization, coincidental with changes in environmental concentration tend to support this view even though the data are limited. Thus the number of sensitized individuals in a TDI plant fell as the average concentration of TDI decreased from 60 ppb in 1956 to less than 4 ppb in 1974 (40). Rates of sensitization of about 60-75% were reported due to exposure to *B. subtilis* enzymes in the detergent industry (29)(48); with environmental control and process changes, the rate is now of the order of 2% (28). Though encouraging, these studies should be interpreted with caution as population selection phenomena could have also played a significant part in reducing the prevalence of occupational rhinitis and asthma in the studied populations.

3. ***Early recognition of sensitization and relocation.*** Bronchial obstruction can be detected by changes in airways resistance (as measured by simple spirometry) often before overt symptoms develop. Thus, evaluation of pre- and post-shift FEV_1 at regular intervals should result in early detection of sensitized workers. Biological monitoring, either by skin tests or *in vitro* serum specific IgE assays, have also been suggested. The correlation of the latter with significant clinical symptomatology, and the fact that their sensitivity is lower than that provided by skin tests, suggest that *in vitro* assays would not detect clinical sensitization earlier than pulmonary function changes. While there is some evidence that positive skin tests may develop before respiratory sensitization (44), this is by no means proven with respect to occupational allergens. Workers should be educated to report respiratory symptoms to the medical representative of their employer, their health and safety representative, and their personal physician. This would contribute to early recognition, yet affected individuals often try to conceal their problems. A major factor in this concealment is the fear of job loss—a very real fear. Some employers attempt to relocate an employee in a part of the plant where exposure to the offending agent does not occur; others terminate the worker's employment, which may lead to litigation. Before any worker education program can be successful, the problems of job security, relocation, and compensation need to be resolved.

4. ***Prevention of reactions in the already sensitized.*** Reduction of environmental concentrations of the agent to levels below which the sensitized individual would react is usually an unachievable ideal. The sensitized worker often responds to concentrations at the level of detectability, and in the context of occupational asthma, the customary industrial hygiene standards of 8-hour time-weighted-averages and ceiling levels are not protective. Prevention of the reaction by continued anti-asthma therapy offers a potential, though nonideal approach. The long-term cost is considerable, therapy may mask the occurrence of chronic effects, and therapy compliance may be poor during asymptomatic periods. Once sensitized, the worker must essentially avoid exposure.

RESEARCH NEEDS

Basic Research

Research efforts are needed to establish the allergic, irritant, or pharmacologic pathogenesis of occupational asthma. Mechanisms involved in the production of late or delayed onset occupational asthma also require elucidation. Additionally, the role of contaminating pollens, mold spores, and other "natural" aeroallergens in organic dusts needs to be clarified in many situations.

Epidemiologic Studies

Considerably more information should be obtained on the prevalence of occupational asth-

ma in many industries. Data on the fate of the occupational asthmatic after ceasing exposure is also needed. Epidemiologic studies should seek to determine not only prevalences of sensitization but the relationship between dose received and the occurrence of sensitization. This can only be achieved by prospective studies with excellent follow-up.

Antigen Characterization

Research needs to be performed in order to characterize and partially purify the natural antigens involved in the production of occupational asthma. Research is also needed to develop suitable preparations for skin tests and *in vitro* tests for circulating IgE antibodies in asthma due to synthetic agents. Only by such research will satisfactory antigens for skin tests and RAST and similar assays be obtained.

Determination of Predisposing Factors

The many predisposing factors that might potentially lead to the development of occupational asthma need to be characterized. These include the presence of pre-existing irritable airways (as defined by methacholine challenge) and the atopic status of the individual (as defined by history and skin reactivity). Such information could be valuable in pre-employment screening designed to reduce the number of high risk individuals.

Education

Medical personnel associated with industry and unions should be made aware of occupational asthma and have both appropriate knowledge and suitable equipment for diagnostic use. Some research into means by which paramedical personnel and unions can be educated in this regard would be desirable.

Centers for Occupational Asthma

It is unlikely that research in the area of occupational asthma caused by so many agents can be carried out in existing small, ill-equipped centers. Thus the support of existing and the creation of new occupational lung disease centers in industrial areas throughout the country would serve as focal points for achieving broad research objectives. The overall goal of these centers should be to apply and adapt the efforts of research development as part of routine medical standards of practice in industry.

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